

## CDER Draft Guidance Document Release Form

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Electronic Submission of CRFs and CRTs Committee, CDER/CBER

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# Guidance for Industry

## Electronic Submission of Case Report Forms and Case Report Tabulations

### **DRAFT GUIDANCE - NOT FOR IMPLEMENTATION**

**This guidance document is being distributed for comment purposes only.**

Draft released for comment on: November 4, 1996.

Comments and suggestions regarding this draft document should be submitted by December 31, 1996. Comments and suggestions received after this date may not be acted upon by the Agency until the document is next revised or updated. For CDER questions regarding this document, contact Kaye Fendt, HFD-103, Center for Drug Evaluation and Research, 5600 Fishers Lane, Rockville, MD 20857 (301-827-3144); or via E-mail at [elcrfcr@cder.fda.gov](mailto:elcrfcr@cder.fda.gov). For CBER questions, contact Mary Buesing, HFM-124, 1401 Rockville Pike, Rockville, MD 20852 (301-827-3726); or via E-mail at [crfcr@A1.cber.fda.gov](mailto:crfcr@A1.cber.fda.gov).

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**GUIDANCE FOR INDUSTRY<sup>1</sup>  
ELECTRONIC SUBMISSION OF CASE REPORT FORMS (CRF)  
AND CASE REPORT TABULATIONS (CRT)**

**I. INTRODUCTION**

Existing Federal regulations require industry to submit applications in a specific form and lists the information required with a submission (e.g., 21 CFR Part 314.50 for new drug applications [NDA] and Part 601.2 for biological product license applications [PLAs] and biologics license applications [BLAs]).<sup>2</sup> For example, the archival copy of an NDA is "required to contain...case report tabulations and case report forms" in addition to an application form, an index, a summary, and various technical sections [21 CFR 314.50(k)(1)]. The regulations also invite applicants to meet with the FDA before submitting an application to discuss the presentation and the format of supporting information [21 CFR 314.50(f)(4)]. If the applicant and FDA agree, the applicant "may submit tabulations of patient data and case report forms in a form other than hard copy...." However, paper copies of the CRFs and CRTs must be submitted with the electronic form unless the requirement for submission of paper copies is waived by the Center Director.

Currently, the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) waive the requirement for a paper submission of CRFs and CRTs on a case-by-case basis if the reviewing division supports the waiver. (See CDER Manual of Policies and Procedures MAPP 6010.1 and CBER OD-R-14-96 Draft.) However, paper copies of the CRFs and CRTs must be maintained by the sponsor [21 CFR 312.57(b)].

In August 1994, the FDA proposed a new regulation, 21 CFR Part 11, Electronic Signatures and Records, that would make it possible for sponsors to submit applications or parts of applications

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<sup>1</sup>This guidance has been prepared by the Electronic Submission of CRFs and CRTs Committee, a joint effort of the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration under the auspices of the CDER Information Technology Coordinating Committee. Although this guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the industry, it does represent the Agency's current thinking on the electronic submission of CRFs and CRTs. An electronic version of this guidance is also available via Internet using the World Wide Web (WWW). To access the document on the WWW, connect to the CDER Home Page at <http://www.fda.gov/cder> and go to the "Regulatory Guidance" section. The CBER WWW site is <http://www.fda.gov/cberftp.html>. A copy of the document may also be obtained via FAX by calling CBER at 1-800-cber-fax or via "bounce-back" e-mail by sending a message to [ecrf@Al.cber.fda.gov](mailto:ecrf@Al.cber.fda.gov).

<sup>2</sup>The term *biologics license application* (BLA) is a new term described in a rule entitled, Elimination of Establishment License Application for Specified Biotechnology and Specified Synthetic Biological Products. This final rule, which was published in the *Federal Register* on May 14, 1996, eliminates the establishment license application (ELA) requirement for certain biotechnology and synthetic biological products subject to licensing under the Public Health Service Act (61 FR 94, pp. 24227-24233).

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in electronic-only form without requesting a specific waiver (59 FR 45160). The proposed rule applies to any paper records required by statute or Agency regulations. In addition, it provides for the Agency to establish a docket on electronic submissions in which the Agency will notify the public when it is ready to accept specific types of electronic submissions. The docket will describe those submissions that may be made in electronic form in whole or in part and identify the corresponding Agency units ready to receive these submissions. The docket also will contain technical guidance on how to make the submission, depending on the receiving unit's capabilities. The Agency expects to finalize the proposed rule soon, and it will take effect five months after final publication.

This guidance for industry on the submission of electronic CRFs and CRTs is one of several currently under development in anticipation of the new regulation on electronic signatures and records. (See also in draft form “Guidance for Industry: Submitting Application Archival Copies in Electronic Format.”). The purpose of the guidance is to provide industry with basic information on how to submit electronic CRFs and CRTs with applications — whether they be NDAs, BLAs, or PLAs — that will be reviewed by CDER or CBER.

As with other guidance documents, FDA does not intend this guidance document to be all-inclusive and cautions that not all information may be applicable to all situations. The guidance document is intended to provide information and does not set forth requirements. The methods and procedures cited in the guidance are suggestions. FDA anticipates that sponsors and investigators may develop alternative methods and procedures and discuss them with the Agency, and the FDA may find those alternative methods and procedures acceptable. Because this is a rapidly developing field, this guidance most likely will be updated periodically.

## **II. PHILOSOPHY**

During the past decade, the Food and Drug Administration (FDA) has gained valuable experience with computer-assisted marketing applications and learned much about the electronic submission process. The Agency has concluded that continuing to rely on untested, customized formats is cumbersome for the Agency and for industry. As a result, the Agency is working to standardize the electronic submission of applications. It is the Agency's goal to establish an approach for submitting electronic applications that creates minimal additional work for sponsors and reviewers, provides maximal flexibility for sponsors and reviewers, and establishes consistency in information transfer requirements across the Agency.

Because it will be impossible to move from paper format to electronic format at once, the Agency is proposing to move from paper regulatory submissions to electronic regulatory submissions in stages. The exact approach presently is under development. The Agency hopes that such an

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approach will allow the Agency to avoid disruptions to the review process while keeping costs to a minimum.

### **III. DEFINITIONS**

**Application:** For the purpose of this document, the term *application* refers to documents submitted under (1) product license applications (PLA), (2) establishment license applications (ELA), (3) biologics license applications (BLA), (4) investigational new drug applications (IND), and (5) new drug applications (NDA). Specific applications are described in detail in 21 CFR 312.23 (IND), 21 CFR 314.50 (NDA), 21 CFR 601 (ELA, PLA), and 61 FR 94, pp. 24227-24233 (BLA).

**Case report form (CRF):** The paper, or electronic, document that serves in whole or in part to meet the requirements of 21 CFR 312.62(b) for investigator record keeping and record retention. The regulatory requirement for submitting CRFs under 21 CFR 314.50(f) can be fulfilled in any of the following ways as it pertains to NDAs; a similar approach should be applied to PLAs and BLAs.

- *Paper CRF:* A paper document consisting of one or multiple pages on which are recorded all clinical, radiologic, laboratory, or other observations, including all modifications, addenda, and corrections, for an individual patient during her/his participation in a clinical study.
- *Electronically imaged CRF:* An exact image or series of images of the paper CRF that contains all original entries with all modifications, addenda, corrections, comments, annotations, and extemporaneous additions.
- *Electronically searchable CRF:* An electronic file (files) of the paper CRF that has all the features of an electronic image plus provides the functionality to search the file/document for character strings and select, save, and print the subsets.
- *Electronically captured CRF (e-CRF):* An auditable permanent data file on a patient, generated through electronic data capture, that contains all data that could be included in either of the above CRF formats.
- *Multi-format:* A combination of both electronic images of paper and electronically captured data.

**Case report tabulation (CRT):** A tabulation of the data for each patient from each study, as defined in 21 CFR 314.50. The regulatory requirement for submitting CRTs under 21 CFR

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314.50(f) can be fulfilled in any of the following ways as it pertains to NDAs; a similar approach should be applied to PLAs and BLAs

- *Paper CRT*: Historically, this has been interpreted to mean **patient line listings** of individual patient study data submitted in multiple appendices. Typical listings include one or all of the following domains of data: demographics, inclusion-exclusion criteria, protocol violations, diagnostic criteria, vital signs, past history, dosing and compliance, concomitant medications, adverse events, outcome measures, outcome parameters. Alternatively, companies have submitted **individual patient profiles**, consisting of one or more pages that collate all the study data for an individual patient.
- *Electronically imaged CRT*: An image of a paper CRT, arranged either as patient line listings or individual patient profile. (NOTE: this type of submission can be indexed by study, appendix, and page number, but does not have the functionality to search by domain and link data.)
- *Electronically functional or electronically analyzable CRT(e-CRT)*: An auditable permanent data file on an individual patient that contains all data and is accessible to common electronic formats including databases, spreadsheets and/or statistical programs.

Data: The information submitted with an application. The word *data* can be used in a number of ways.

- *All data*: All the clinical data that were collected on a subject or a patient, including annotations and extemporaneous additions.
- *Database Index*: Information included with an electronic database that enables a person using the database or software accessing the database to efficiently search for specific records.
- *Derived data*: Calculated information, such as study duration based on start and stop dates, log (response), and log (dose).
- *Domain of data*: A grouping of related data elements. Typical domains of data include one or more of the following: demographic data, inclusion-exclusion criteria; data on diagnoses, dosing, and compliance; data on concomitant medications, concurrent illnesses, and adverse events; and laboratory data; data on vital signs; and data on protocol violations.
- *Electronic data*: Data from clinical studies that can be analyzed or manipulated using commonly available software. Electronic data include not only the data collected during

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the study, but also the meta data describing the process of collection, validation, error handling procedures, and analytical assumptions.

- *Interpreted data* (subjective): Interpretation of the objective data. Examples include outcome variables such as cure, success/failure, and evaluability. The interpretation of the data may differ depending on who is reviewing it.
- *Meta data*: Information that describes the data environment sufficiently to allow the analyst/reviewer/software to use the data appropriately and effectively.
- *Observed data* (objective, raw, original, validated): Factual information and observations collected during a clinical study (e.g., date, age, weight, height, vital signs, laboratory results, sign and symptoms, test scores, radiographic data). Data that enable a sponsor or reviewer independently to evaluate and determine the patient's qualifications for participating in a study as well as the outcome of therapy. These data are frozen (i.e., cannot be changed).

Electronic archives: Electronic files that preserve the validated data in a durable form for later retrieval. These files should be tamper-resistant and contain an **exact** duplicate of all the information submitted for review of the application.

Electronic paper: An exact image of a paper document.

Paper submission: A regulatory submission made in part or in whole on paper.

Regulatory submission: Any document submitted to the FDA that either is or may become the basis for a regulatory action by the Agency. Historically, submissions have been made in paper format; currently the format is evolving from paper to electronic.

Table: A summarized presentation of data that facilitates the comparison of groups.

Tabulation: A CRT, the presentation of the captured data for archival and review.

## **IV. ELECTRONIC SUBMISSION OF CRFs AND CRTs**

### **A. Case Report Forms (CRF)**

*Electronically imaged* CRF files should function at a minimum like their paper

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counterparts. Under the current regulation [21 CFR 314.50(f)(2)], an NDA “must contain copies of individual CRFs for each patient who died during a clinical study or who did not complete the study because of an adverse event, whether believed to be drug related or not...” The CRF includes patients receiving reference drugs or placebo. The requirement for CRFs may be waived by FDA for specific studies if the case report forms are unnecessary for a proper review of the study. The regulation states further that the applicant “must submit to FDA additional case report forms and tabulations...as requested by the director of the FDA division responsible for reviewing the application”[21 CFR 314.50(f)(3)].

CRFs are ordinarily submitted as part of PLAs and BLAs. CBER will consider waiving specific CRFs according to the policy outlined in CBER OD-R-14-96 Draft.

Electronically imaged CRFs should generally contain the following primary features.

1. *A comprehensive index or table of contents*— for easy location of an individual patient’s CRF including hypertext links between the table of contents and individual studies, sites/investigators, individual patient IDs, and data domain (frequently searched for by CRF page number).
2. *Ability to read and print each page exactly as it would have been printed in a paper submission.* Fonts should be retained as should the legibility of the written text as well as any special orientation or pagination.
3. *Ability to create hypertext linking and bookmarks*— to write notes linked to pages that subsequently can be found and summarized, and to copy images, notes, or bookmarks for transfer to the review document.
4. *Accessibility* on any computer platform.
5. *A format* that is commonly available and requires minimal training.

*Electronically searchable submissions* should offer the same types of information as electronically imaged CRFs, and the following functions would be useful:

6. *Ability to search* for a character string or multiple character strings.

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7. *Ability to select and save a subset* of CRFs through character string searches. These subsets should then be searchable for character strings.
8. *Ability to print* selected CRFs.
9. *Ability to view* the audit trail for selected CRFs.

When formatting, cataloging, and indexing electronic CRFs, we recommend that Acrobat PDF<sup>3</sup> be produced from direct computer output or from image files. All files for a single study should be placed in a single directory, and all patient-specific forms should be placed in a single file. During production of the CRFs, the Acrobat indexing fields should be completed using:

- title field: the clinical study designator
- author field: the pharmaceutical name and application number
- subject field: the unique patient I.D. number
- keywords field: relevant events (e.g., death, dropout, pregnancy)

No full-text indexing is necessary when the data format meets the above specifications. Adobe Catalog should be used to create indexes of the field data. These indexes should be submitted along with the document files. Identical study and patient designators should be used for both CRFs and CRTs.

### **B. Case Report Tabulations (CRT)**

Under 21 CFR 314.50(f)(2), the NDA is required to contain tabulations of the data from each adequate and well-controlled study under 314.126 (Phase 2 and Phase 3 studies as described in 312.21 (b) and (c) of this chapter), tabulations of the data from the earliest clinical pharmacology studies (Phase 1 studies as described in 312.21(a) of this chapter), and tabulations of the safety data from other clinical studies. The tabulations are required to include the data on each patient from each study, except that the applicant may delete those tabulations that the Agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness.

Under CBER policy, CRTs ordinarily are submitted as part of PLAs and BLAs. CBER will consider waiving specific CRTs on a case-by-case basis.

*Electronically imaged* CRT files should generally contain the following primary features:

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<sup>3</sup>FDA use of specific products does not constitute an endorsement of that product.

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1. *A comprehensive index or table of contents*— for easy location of an individual patient's CRF, including hypertext links that link the table of contents to individual studies, a site or investigator, individual patient IDs, and specific data domains.
2. *Ability to navigate through the electronic document* using the standard table of contents currently being provided with paper copy submissions to locate individual patients in studies and individual domains of data across patients.
3. *Ability to create hypertext linking and bookmarks*— to write notes linked to pages that can subsequently be found and summarized, and copy images for transfer to the review document.
4. *Accessibility* on any computer platform.
5. *An audit trail of any changes to the original data.*

*Electronically functional CRTs* (i.e., electronic data) should include the following:

6. *All observed and interpreted data* in datasets arranged as flat files.
7. *All variables* derived to perform specific analyses presented in the application. For example, if an analysis on the LOCF (last observation carried forward) for an outcome measure is presented in the application study report, include the calculated value of the LOCF measure in a column in the appropriate dataset.
8. *An index* listing all datasets in the submission. The file name and a full narrative description in document format should be included.
9. *A single dataset* for each domain of the data collected in the CRF for each study.
10. *A unique patient ID number* provided for each subject in the application.
11. *The patient ID* included as one of the first variables in each dataset.
12. *Variables* common to different datasets should have the same variable names across the datasets. This is appropriate for combining data across the different datasets and for quality assurance in research data management practices.
13. *A CRF* in tabular form with the rows containing all protocol study data variables, such as duration between initial dose administration and the time the data are calculated.

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14. *A full description of the variables.* Include the variable name, variable description used in the dataset, a narrative description of the variable including the type of variable (date, character, number) and a definition of all abbreviations used in the columns. Provide the description in the document format.
15. *All datasets* should be importable to standard commercial off-the-shelf (COTS) data management and statistical packages (e.g., SAS, EXCEL, BMDP).
16. *CRFs and CRTs* should be stored on ISO 9660 CD-ROM and submitted to CDER's or CBER's central document control room. (See also draft "Guidance for Industry: Submitting Application Archival Copies in Electronic Format.")
17. *Files should be accessible* using commonly available hardware platforms. (See draft "Guidance for Industry: Submitting Application Archival Copies in Electronic Format.")

When formatting, cataloging, and indexing electronic CRTs, we recommend that CRTs be submitted in Adobe Acrobat PDF — the ASCII output may be printed through the Acrobat PDF Writer to produce the desired files. All files for a single study should be placed in a single directory. If possible, all patient-specific output should be placed in a single file. During production, the Acrobat indexing fields should be completed using:

- title field: the clinical study designator
- author field: the pharmaceutical name and application number
- subject field: the unique patient I.D. number
- keywords field: relevant events (e.g., death, dropout, pregnancy)

No full-text indexing is necessary when the data format meets the above specifications.

If all patient-specific data are output to a single file, bookmarks may be placed for each patient. With bookmarks, the Acrobat indexing fields should be completed using:

- title field: the clinical study designator
- author field: the pharmaceutical name and application number
- subject field: **no data**
- keywords field: relevant events (e.g., death, dropout, pregnancy)

No full-text indexing is necessary when the data format meets the above specifications.

If bookmarks are not placed for individual patients, the Acrobat indexing fields should be

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completed using:

- title field: the clinical study designator
- author field: the pharmaceutical name and application number
- subject field: **no data**
- keywords field: relevant events (e.g., death, dropout, pregnancy)

However, full-text indexing should be provided when the data format meets these specifications.

In all cases, Adobe Catalog should be used to create indexes of the field and full-text data, when appropriate. These indexes should be submitted along with the document files.